HEPLISAV-B

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HEPLISAV-B Antigen Similar to Current HBV Vaccines

- Contains yeast-derived recombinant hepatitis B surface antigen
- Adjuvant
  - HEPLISAV-B uses Toll-like receptor 9 (TLR9) agonist, 1018
  - Currently licensed vaccines use alum
- Sterile, liquid dosage form in 0.5 mL dose vials
  - 20 µg HBsAg
  - 3 mg 1018
- Administered: 2 doses over 1 month
  - Compared to 3 doses over 6 months

1018 Adjuvant

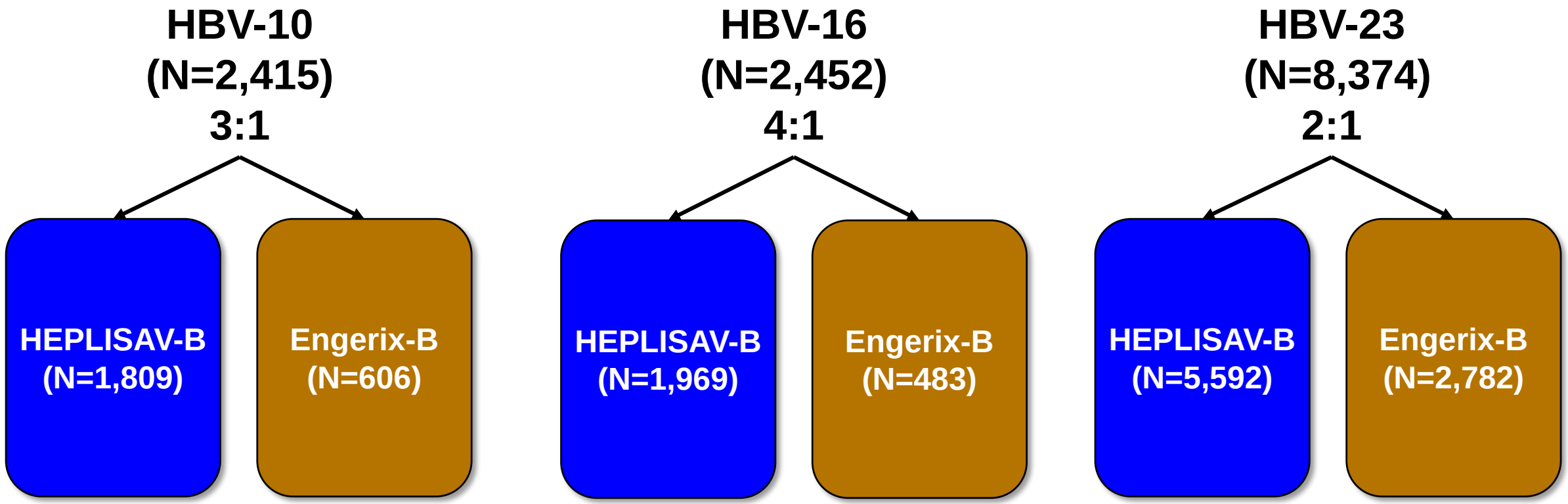
- Small synthetic oligonucleotide with immunostimulatory CpG motifs
- Mimics natural innate immune response to bacterial and viral DNA
- Enhances B and T cell responses to co-administered vaccine antigens
- 1018 targets well-characterized cellular receptor
  - TLR9

Proposed Indication for HEPLISAV-B

- Active immunization against infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older.
- PDUFA action date - November 9

Immunogenicity

Pivotal Studies
HBV-10, HBV-16 and HBV-23



Randomized population

Common Study Design Features

- Observer-blinded, randomized, active-controlled, multi-center
- Exclusions
  - Current or previous hepatitis B infection or hepatitis B vaccine
  - HIV infection, immunosuppression, or history of autoimmune disease
- Seroprotection rate (% with anti-HBs ≥ 10 mIU/mL) compared with Engerix-B
- Anti-HBs levels measured by approved standardized assay (Ortho Vitros ECi)

Study Statistics

Primary

Demonstrate non-inferiority of HEPLISAV-B SPR to Engerix-B at primary endpoint (in subjects with diabetes mellitus in HBV-23)

Non-inferiority Criterion

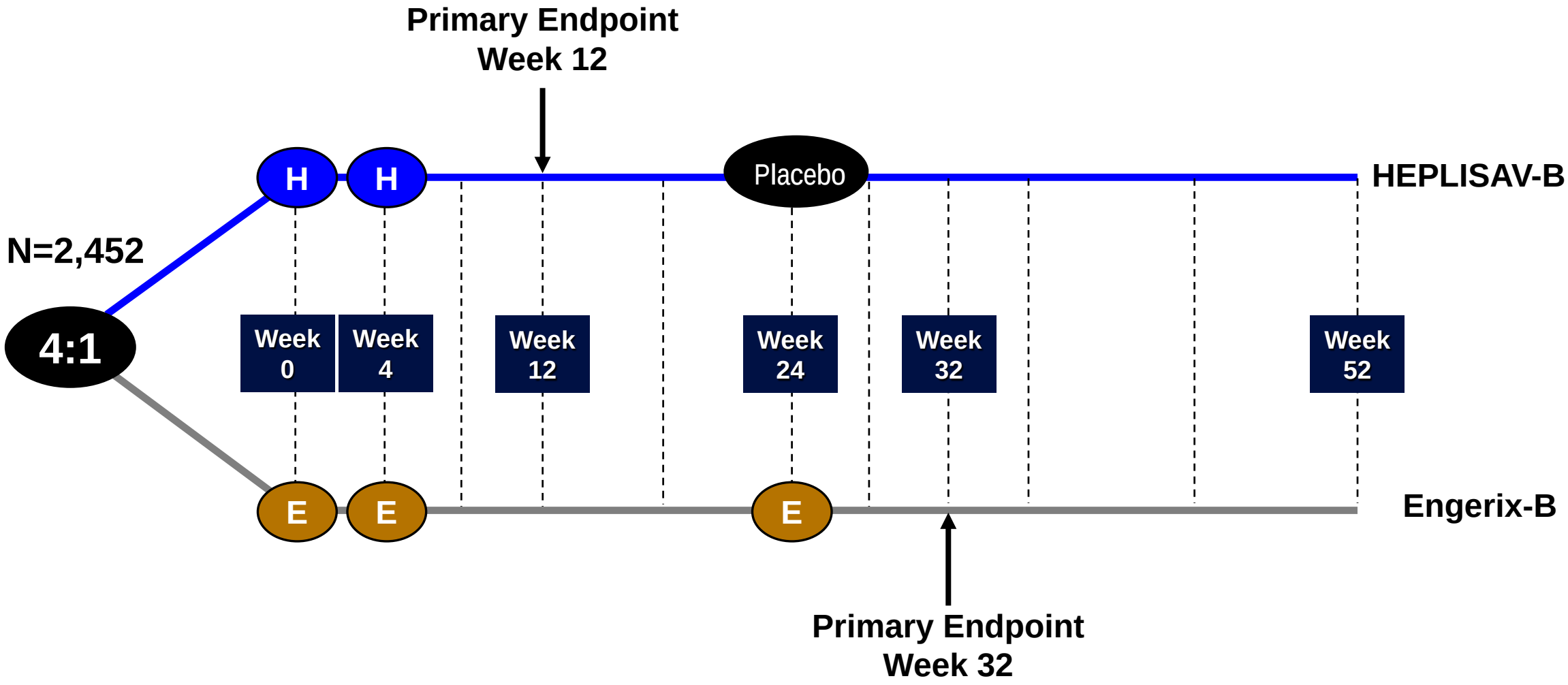
HEPLISAV-B non-inferior to Engerix-B if lower limit of 95% confidence interval of the difference in SPRs was greater than -10%.

Statistical Significance Criterion

If HEPLISAV-B seroprotection was non-inferior, then HEPLISAV-B seroprotection was considered statistically significantly higher if lower limit of 95% confidence interval was greater than 0.

Per-protocol population used in analyses.

Illustrative Study Design (HBV-16) (40 – 70 Years, United States and Canada)

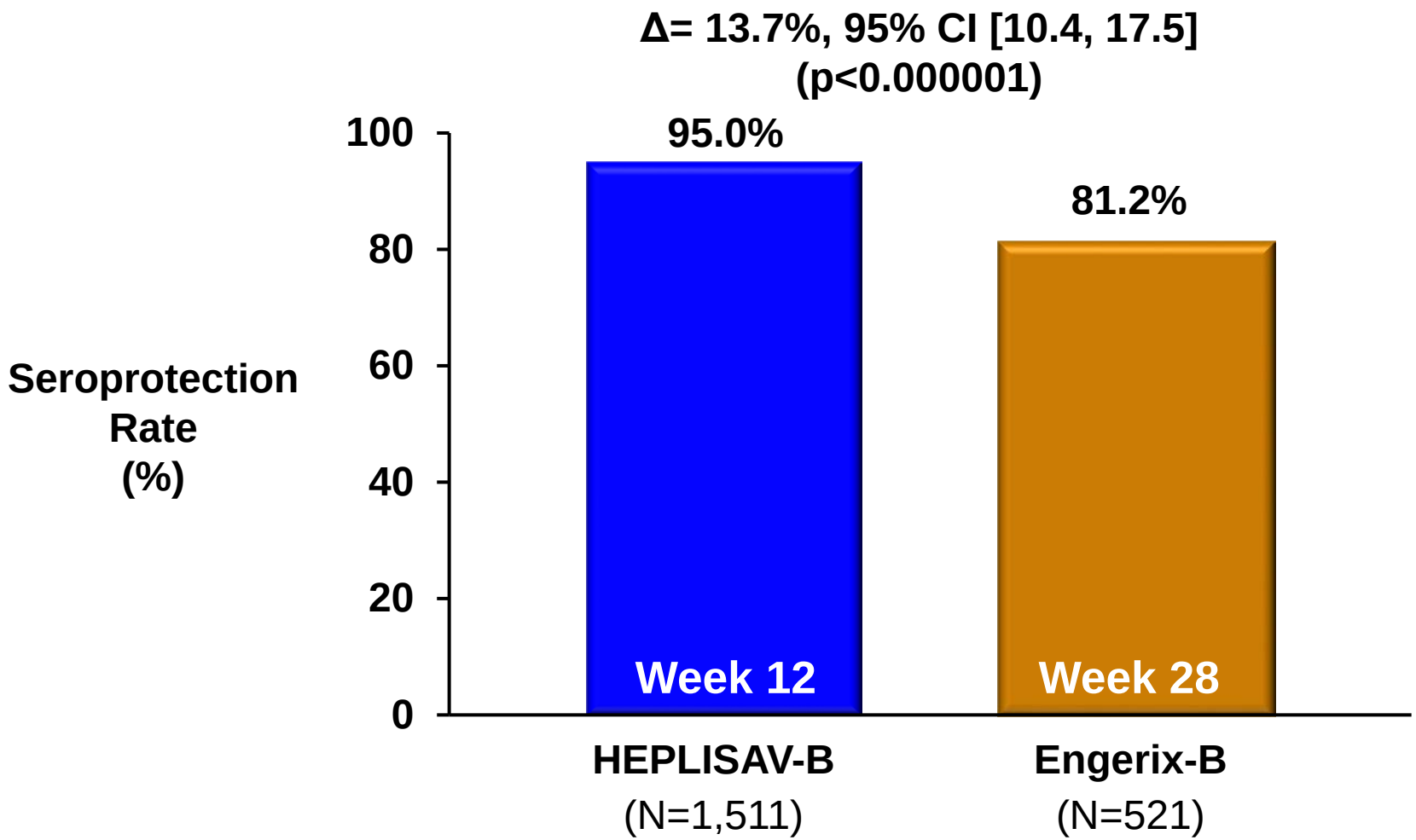


Demographic and Baseline Characteristics

Trial	HBV-10		HBV-16		HBV-23	
Subgroup	18 to 55 Years		40 to 70 Years		18 to 70 Years	
Per-Protocol Population	HEPLISAV-B (N = 1557)	Engerix-B (N = 533)	HEPLISAV-B (N = 1123)	Engerix-B (N = 359)	HEPLISAV-B (N =4537)	Engerix-B (N = 2289)
Mean Age (SD)	40.2 (9.25)	40.4 (8.87)	53.9 (7.80)	54.3 (7.85)	51.0 (11.53)	50.9 (11.40)
Sex						
Men	46.2%	42.0%	47.7%	49.6%	50.3%	50.2%
Race						
White	94.1%	92.3%	83.2%	84.4%	70.9%	73.2%
Black	1.8%	3.3%	14.5%	13.3%	26.3%	24.2%
Asian	2.3%	3.1%	1.1%	0.6%	1.0%	1.3%
Other	1.9%	1.3%	1.2%	1.7%	1.8%	1.4%
BMI > 30 kg/m^2	24.4%	27.6%	44.0%	42.8%	49.5%	47.0%
Smoker	35.6%	36.3%	20.3%	20.7%	31.1%	31.1%

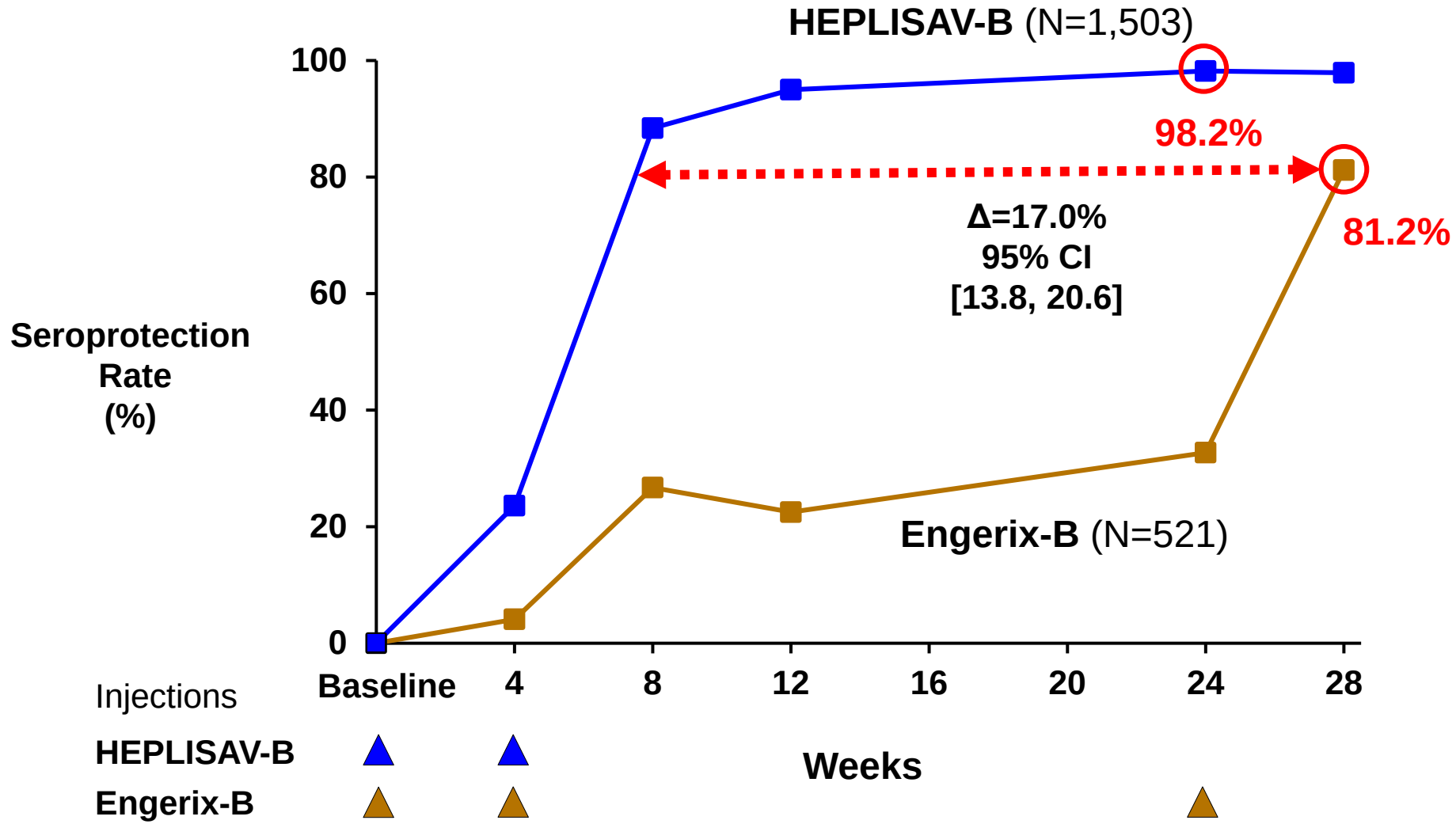
Per-protocol population

HBV-10: HEPLISAV-B Met Primary Endpoint



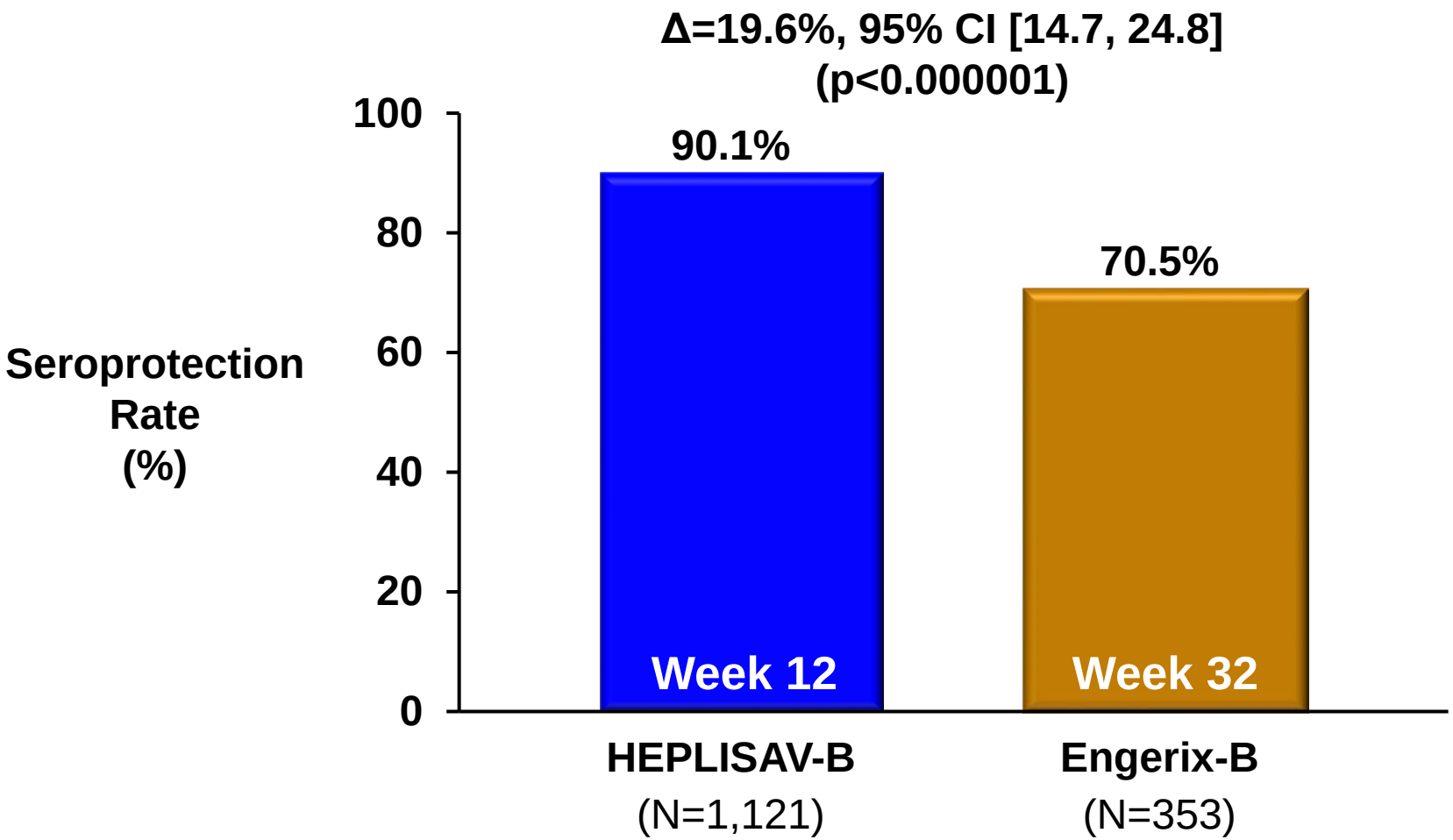
Per-protocol population

HBV-10: HEPLISAV-B Induced Significantly Higher Peak SPR



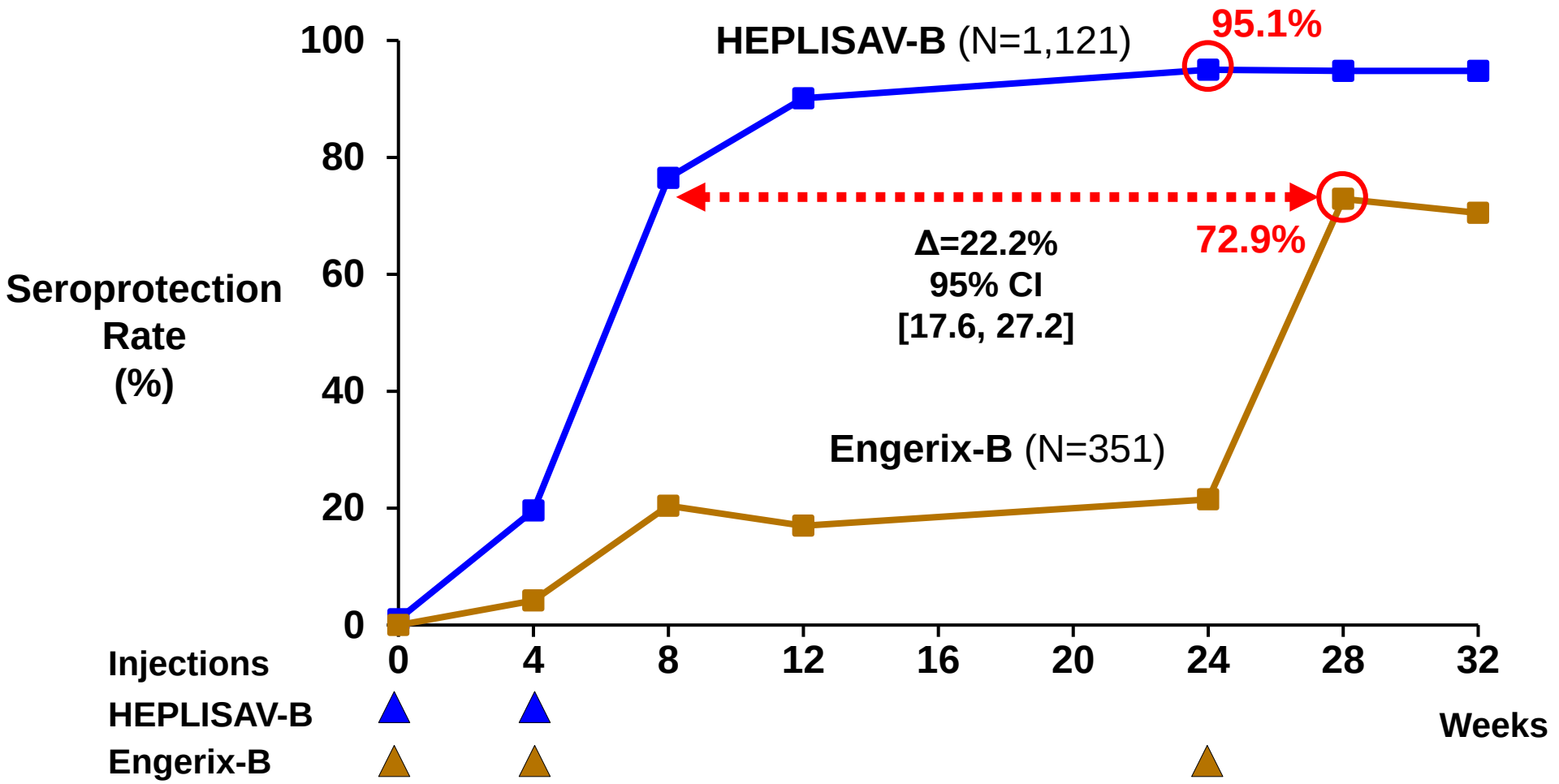
Per-protocol population

HBV-16: HEPLISAV-B Met Primary and Secondary Endpoints



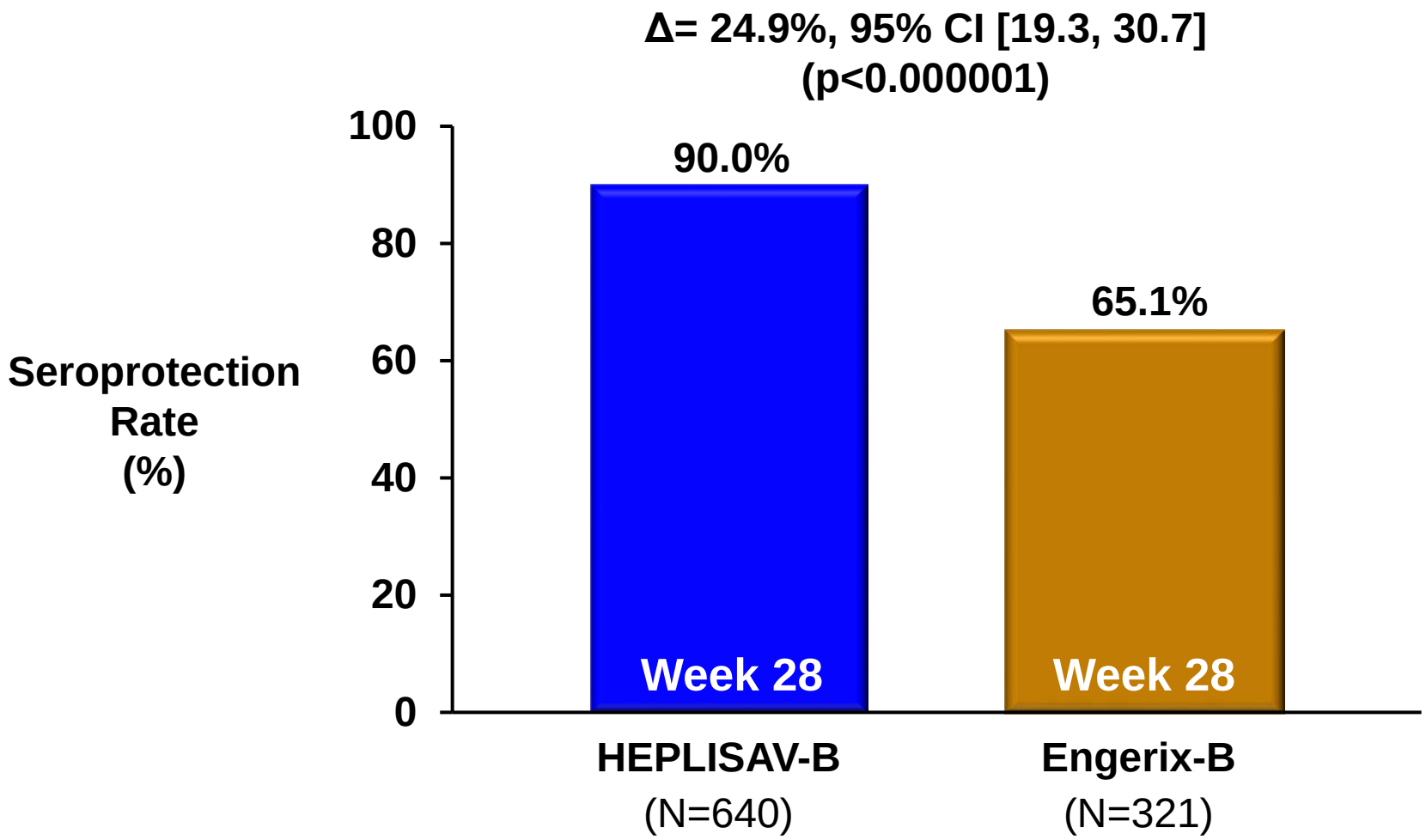
Per-protocol population

HBV-16: HEPLISAV-B Induced Significantly Higher Peak SPR



Per-protocol population

HBV-23: HEPLISAV-B Met Primary Endpoint in Type 2 Diabetes Mellitus



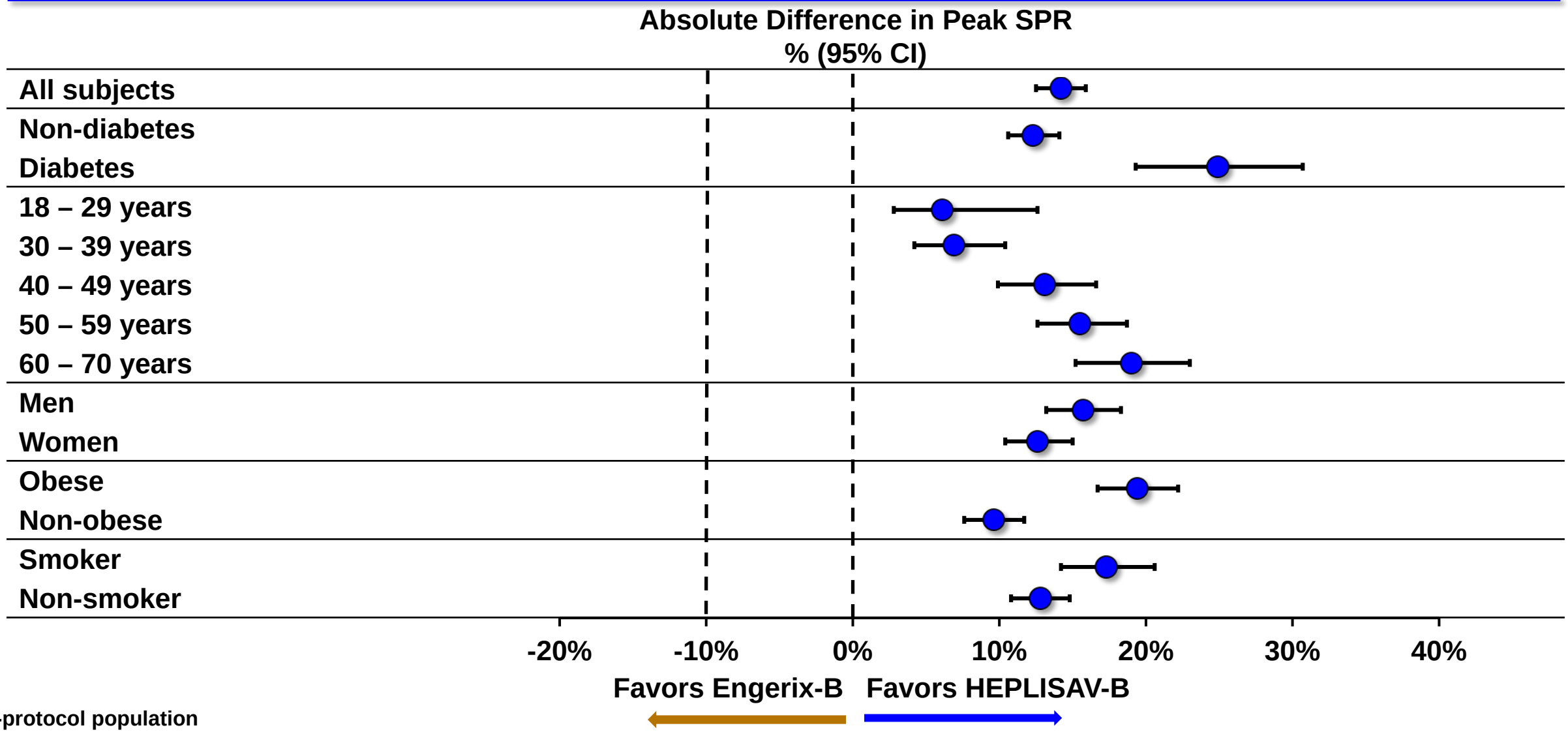
Per-protocol population

HBV-23: Higher Seroprotection Rates for HEPLISAV-B in Prespecifed Populations

	HEPLISAV-B N	Engerix-B N	Peak SPR (%)	
			HEPLISAV-B	Engerix-B
Total population	4,376	2,289	95.4%	81.3%
Non-diabetes	3,762	1,968	96.2%	83.9%
Diabetes	640	321	90.0%	65.1%
18 – 29 years	174	99	100.0%	93.9%
30 – 39 years	632	326	98.9%	92.0%
40 – 49 years	974	518	97.2%	84.2%
50 – 59 years	1,439	758	95.2%	79.7%
60 – 70 years	1,157	588	91.6%	72.6%
Men	2,203	1,150	94.5%	78.8%
Women	2,173	1,139	96.4%	83.8%
Obese	2,165	1,076	94.7%	75.4%
Non-obese	2,208	1,212	96.1%	86.6%
Smoker	1,371	711	95.9%	78.6%
Non-smoker	3,005	1,578	95.2%	82.4%

Per-protocol population

HBV-23: Differences in SPR Statistically Significant in Prespecified Subgroups



Per-protocol population

Summary of HEPLISAV-B Immunogenicity

- Met primary objective of non-inferiority as well as secondary endpoint of statistical significance in healthy subjects and in subjects with diabetes
- Significantly higher SPRs at early time points
- Significantly higher SPRs at peak
- Significantly higher SPRs in all adult groups

Safety

Safety Populations in HEPLISAV-B Pivotal Studies

Population	HEPLISAV-B	Engerix-B	Assessments
HBV-10 and HBV-16	3,778	1,086	Reactogenicity, AEs
HBV-23	5,587	2,781	Medically-attended AEs (MAEs)
Primary safety population (PSP) (HBV-10, HBV-16, HBV-23)	9,365	3,867	Deaths, SAEs Immune-mediated AEs

HEPLISAV-B Safety Profile Similar to Engerix-B

	HEPLISAV-B %	Engerix-B %
HBV-10 and HBV-16	**N=3,778**	**N=1,086**
Any post injection reaction (PIR)[a]	55.1	57.1
Any AE	55.3	58.1
HBV-23	**N=5,587**	**N=2,781**
Any MAE	46.0	46.2

For PIRs HEPLISAV-B N= 3,777 and Engerix-B N= 1,086.
One subject in HBV-10 erroneously included in Engerix-B was correctly included in HEPLISAV-B group in the PSP.

Post-Injection Reactions (PIR) Balanced Between HEPLISAV-B and Engerix-B

HBV-10 and HBV-16	HEPLISAV-B N=3,777 %	Engerix-B N=1,087[a] %
Any solicited PIR	55.1	57.1
Local PIR	42.8	41.1
Pain	41.7	40.5
Redness	3.7	1.1
Swelling	2.4	1.3
Systemic PIR	32.3	37.4
Fatigue	21.4	25.1
Headache	20.1	25.3
Malaise	13.8	16.0
Fever ≥ 38°C	1.7	3.4

a. One subject in HBV-10 erroneously included in Engerix-B was correctly included in HEPLISAV-B group in the PSP.

HEPLISAV-B Safety Profile Generally Similar to Engerix-B in Primary Safety Population

PSP (HBV-10, HBV-16 and HBV-23)	HEPLISAV-B N=9,365 %	Engerix-B N=3,867 %
Deaths	0.28	0.21
SAEs	4.8	4.8
Any new-onset immune-mediated AE	0.20	0.13

Type and Frequency of SAEs Generally Similar Between HEPLISAV-B and Engerix-B

PSP (HBV-10, HBV-16 and HBV-23) Preferred Term	HEPLISAV-B N=9,365 %	Engerix-B N=3,867 %
At least 1 SAE	4.8	4.8
Pneumonia	0.17	0.21
Osteoarthritis	0.17	0.13
Acute myocardial infarction	0.17	0.05
Non-cardiac chest pain	0.13	0.21
Chronic obstructive pulmonary disease	0.11	0.10
Cellulitis	0.07	0.10
Prostate cancer	0.04	0.18

Acute Myocardial Infarction (HBV-10, HBV-16, and HBV-23)

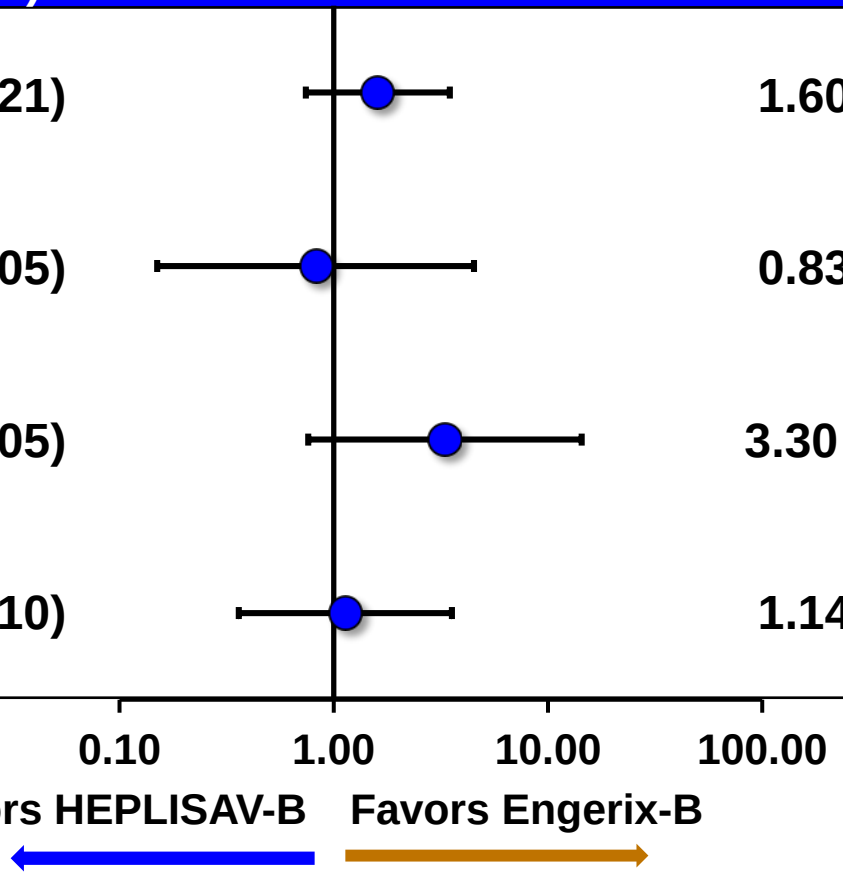
Study	HEPLISAV-B n/N	HEPLISAV-B %	Engerix-B n/N	Engerix-B %	Relative Risk	95% CI
HBV-23	14/5587	0.25%	1/2781	0.04%	6.97	(0.92, 52.97)
HBV-16	2/1968	0.10%	1/481	0.21%	0.49	(0.04, 5.38)
HBV-10	0/1810	0	0/605	0	N/A	N/A

Strategy to Explore Myocardial Infarction Imbalance

- Identification and post-hoc, blinded adjudication of potential atherosclerotic outcomes
- 3-point Major Adverse Cardiovascular Events (MACE)
  - Cardiovascular death
  - Myocardial infarction
  - Stroke
- Evaluation of events:
  - Risk factors among those with MACE outcomes
  - Comparison of observed rates with expected
  - Temporal relationship of events to vaccine administration

Adjudication-Confirmed 3-Point MACE Outcomes

PSP (HBV-10, HBV-16, HBV-23)	HEPLISAV-B N=9,365 n (%)	Engerix-B N=3,867 n (%)	Relative Risk (95% CI)
Composite 3-point MACE	31 (0.33)	8 (0.21)	1.60 (0.74, 3.48)
Death from CV events	4 (0.04)	2 (0.05)	0.83 (0.15, 4.51)
Myocardial infarction	16 (0.17)	2 (0.05)	3.30 (0.76, 14.36)
Stroke	11 (0.12)	4 (0.10)	1.14 (0.36, 3.56)



Prevalent Risk Factors Among Subjects with MACE

PSP (HBV-10, HBV-16 and HBV-23)	MACE N=39		Primary Safety Population HEPLISAV-B N=9,365	Primary Safety Population Engerix-B N=3,867
Age - median in years (range)	60 (39-70)		50 (18-70)	50 (18-70)
Medical condition	n	%	%	%
Hypertension	29	74.4	29.8	30.5
Diabetes mellitus	8	20.5	10.3	11.0
Hyperlipidemia	10	25.6	10.9	11.8
Obesity	18	46.2	43.2	42.8
Smoking	11	28.2	31.3	32.4

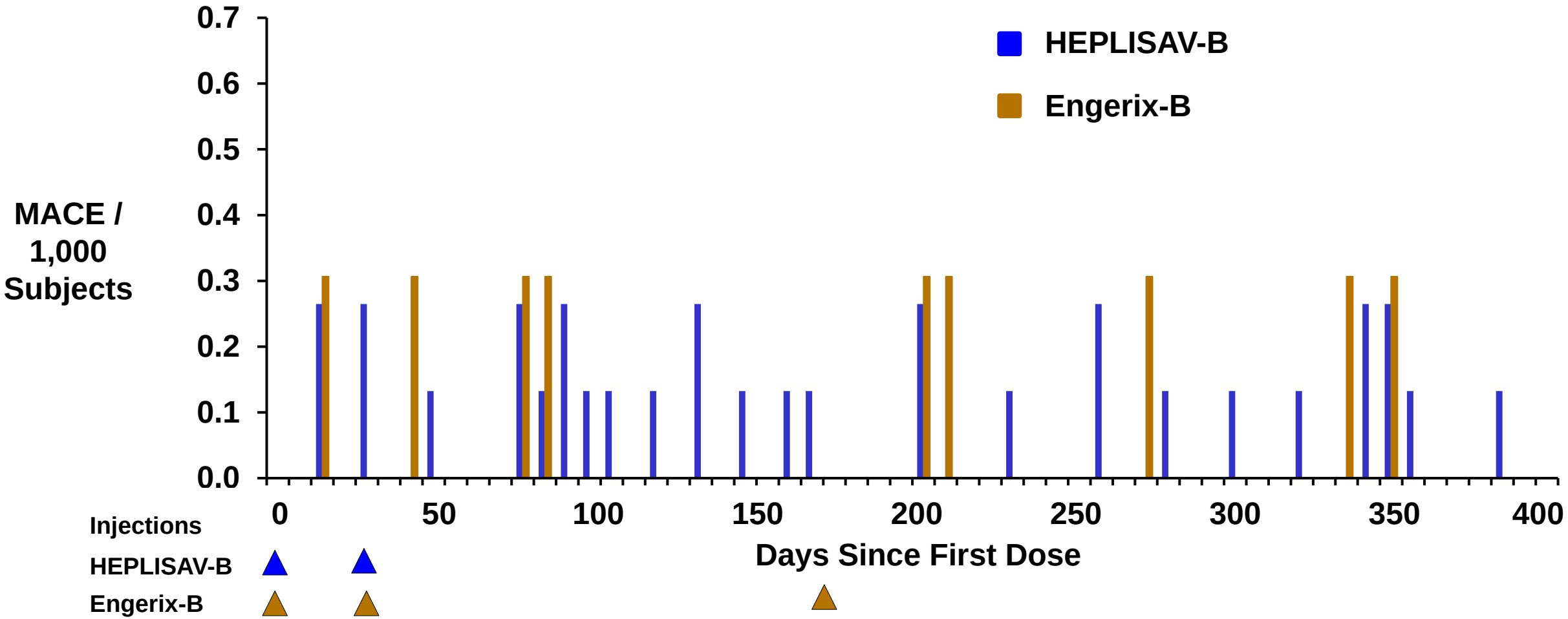
Age-, Sex-, and Race-Adjusted Incidence of Confirmed 3-Point MACE Lower than Expected

	HEPLISAV-B N=6,724 p-y	Engerix-B N=2,903 p-y	Expected Rate
	1,000 p-y	1,000 p-y	1,000 p-y
Observed 3-point MACE	4.6	2.8	6.5
Observed cardiovascular deaths	0.6	0.7	1.6[1]
Observed myocardial infarction	2.4	0.7	2.6[2]
Observed stroke	1.6	1.4	2.3[3]

Black and white subjects in HBV-16 and HBV-23.

1. Vital statistics 2. Atherosclerosis Risk in Communities Surveillance 3. Greater Cincinnati/Northern Kentucky Stroke Study

MACE Occurred Throughout Trials



Primary safety population

Cardiovascular Conclusion

- No biologically plausible explanation for imbalance
- Lack of consistency across trials
- CV events occurred at expected rates in patients with CV risk
- No temporal association

New-Onset Immune-Mediated Events

PSP (HBV-10, HBV-16 and HBV-23)	HEPLISAV-B N=9,365		Engerix-B N=3,867	
	n	%	n	%
New-onset immune-mediated	19	0.20	5	0.13
Bell's palsy	6	0.06	2	0.05
Hypothyroidism	3	0.03	0	0
Other	10	0.11	3	0.08

Rare Serious Immune-Mediated Events Balanced Between Groups

Study	AESI	Time Since Last Dose (months)
HEPLISAV-B		
HBV-10	c-ANCA vasculitis (Granulomatosis with polyangiitis)	2.4
HBV-10	Guillain-Barré syndrome ▪ 5 days after influenza vaccine	3.7
HBV-16	Cavernous sinus syndrome ▪ Tolosa-Hunt syndrome not confirmed by radiology	8.5
Engerix-B		
HBV-10	p-ANCA vasculitis (Microscopic polyangiitis)	4.2

Primary safety population, randomization ratio of 2.4 : 1

Similar Autoantibody Development in HEPLISAV-B and Engerix-B Groups

ANCA

- HEPLISAV-B: N =1972; Engerix-B: N = 596
- No confirmed positive result

ANA

- HEPLISAV-B: N = 4164; Engerix-B: N = 1209
- 5.5% of HEPLISAV-B and 5.1% of Engerix-B recipients developed antibodies

Anti-dsDNA

- HEPLISAV-B: N = 4117; Engerix-B: N = 1177
- 1.2% of HEPLISAV-B and 1.0% of Engerix-B recipients developed antibodies

Antiphospholipid antibodies (HBV-23 Laboratory Substudy, N=309)

- No difference in anti-cardiolipin IgM or IgG, lupus anticoagulant, anti-beta2 glycoprotein 1 IgG
- Transient increase in anti-beta2 glycoprotein 1 IgM at Week 8 in 7.7% of HEPLISAV-B and 1.0% of Engerix-B recipients

Safety Summary – Similar to Engerix-B

- Similar rates of post-injection reactions, AEs / MAEs
- SAEs similar with imbalances in individual terms
  - Acute MI for HEPLISAV-B
  - Prostate cancer for Engerix-B
- No evidence for an increase in the rate of any single immune-mediated event
- Autoantibody conversions balanced

Post-Marketing Surveillance Studies at Kaiser Permanente Southern and Northern California

- Electronic Medical Record analysis
  - Acute myocardial infarction (Southern region)
    - 25,000 HEPLISAV-B: 25,000 other hepatitis B vaccine
    - Non randomized cluster design
  - Immune-mediated events (Southern and Northern regions)
    - 30,000 HEPLISAV-B: 30,000 other hepatitis B vaccine

HEPLISAV-B Conclusions

- Induces high rates of seroprotection in all adults
  - Including populations with reduced response to current vaccines
- Provides earlier seroprotection
- Similar safety profile
- Should increase adherence with 2-dose schedule over 1 month

Cost-effectiveness

Vaccine 31 (2013) 4024–4032

Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Cost-effectiveness of hepatitis B vaccination using HEPLISAV™ in selected adult populations compared to Engerix-B® vaccine

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		Patients with Diabetes	Healthcare Workers	Travelers
HEPLISAV-B ($100)	Discounted Cost	$25,373,976	$120,183,203	$26,225,377
	Discounted QALY	1,442,023	2,799,372	2,799,206
Engerix-B ($52.50)	Discounted Cost	$23,584,710	$119,466,431	$24,934,339
	Discounted QALY	1,441,881	2,799,307	2,798,974
	Incremental Cost	$1,789,266	$716,772	1,291,038
	Incremental QALY	142	65	232
	ICER	**$12,613**	**$11,062**	**$5,564**

Table was adapted from published article

Potential Public Health Benefit of 2 Dose HEPLISAV-B

- HEPLISAV-B may reduce impact of low adherence in high-risk adults
- For example:
  - Estimates of effective (“real world”) SPR calculated by adjusting SPRs after each dose in HEPLISAV-B trials using adherence data in 18-39 year old MSM from Gunn study in STD clinic
  - Estimated effective SPR in 18-39 year old MSM:
    - HEPLISAV-B: 76%
    - Engerix-B: 47%.
    - Difference in “real world” SPRs = 29%
    - Difference in clinical trial SPRs = 10%

Additional Benefit of HEPLISAV-B in Averting Hepatitis-B Related Health Outcomes in Patients with Diabetes

Condition Prevented	CDC Estimate for Engerix-B[1]	Estimate Using HEPLISAV-B*	Added Benefit from HEPLISAV-B	Benefit applied to ~50% of unvaccinated patients (~5,000,000)
Infection	4,271	7,359	3,088	29,000
Hospitalization	467	805	338	3,200
Chronic hepatitis B	256	441	185	1,800
HCC	33	57	24	220
Liver transplant	13	22	9	80
Death	130	224	94	900

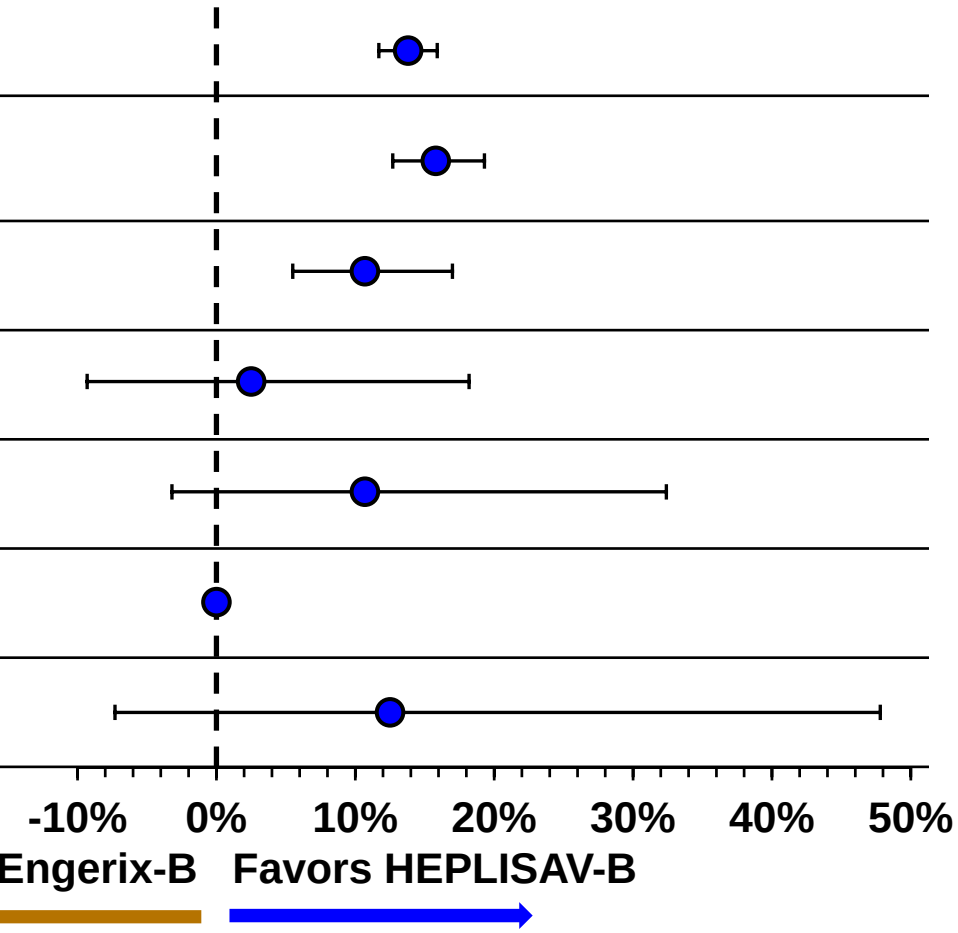
- HEPLISAV-B provides ~72% decrease in hepatitis B related outcomes

*Assumptions: Vaccine Safety Datalink adherence rates[2]; SPRs in HEPLISAV-B clinical trials; HCC= hepatocellular carcinoma

1. Hoerger, 2013. 2. Nelson, 2013

HBV-23: Seroprotection Rates by Race and Ethnicity Consistent Across Groups

Race	HEPLISAV-B N	HEPLISAV-B SPR (%)	Engerix-B N	Engerix-B SPR (%)
White	3084	94.4	1675	80.6
Black	1169	98.1	554	82.3
Hispanic or Latino	391	94.9	183	84.2
Asian	45	95.6	29	93.1
Native American	46	95.7	20	85.0
Pacific Islander	12	100.0	3	100.0
Other	18	100.0	8	87.5

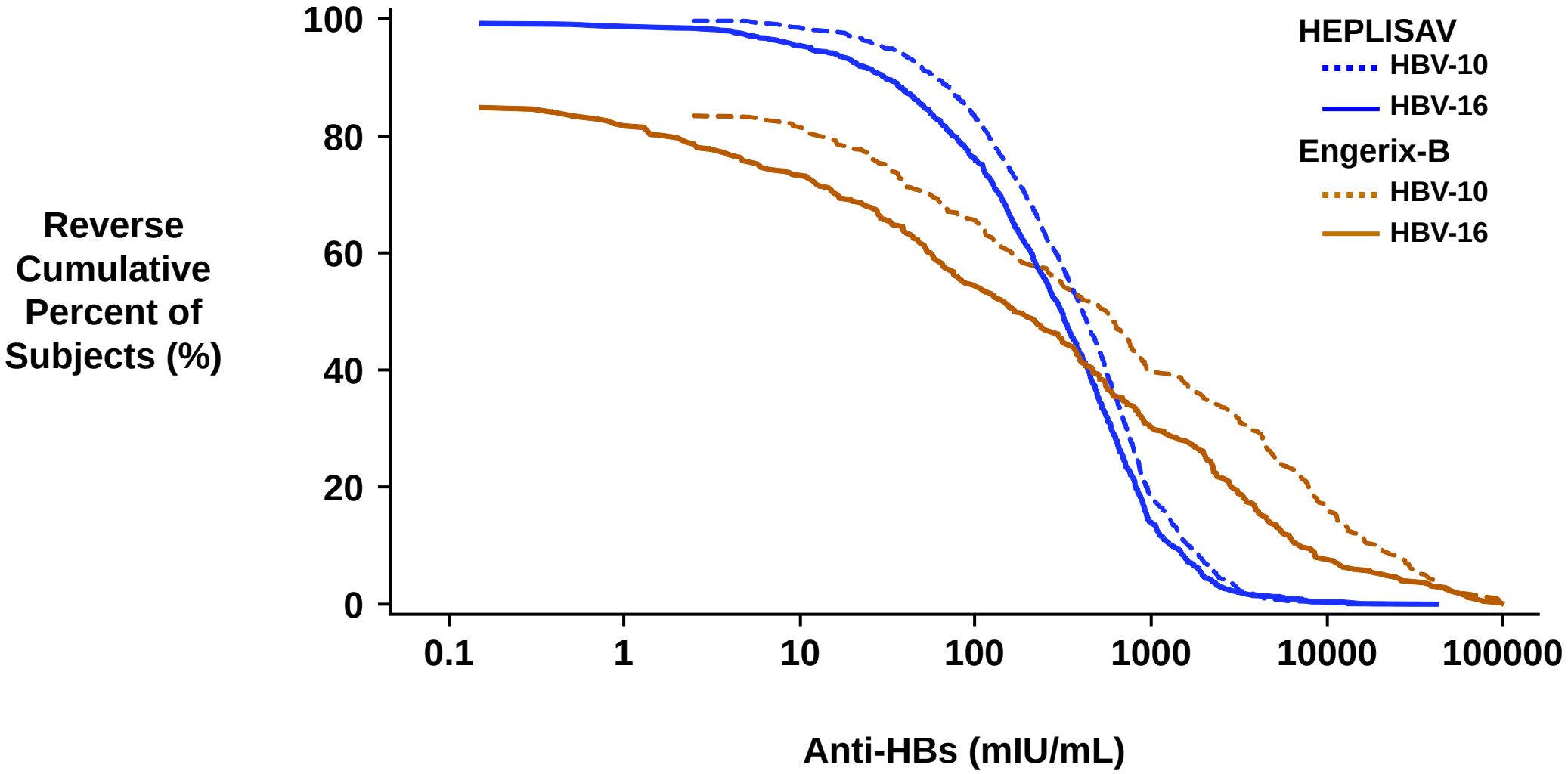


Per-protocol population

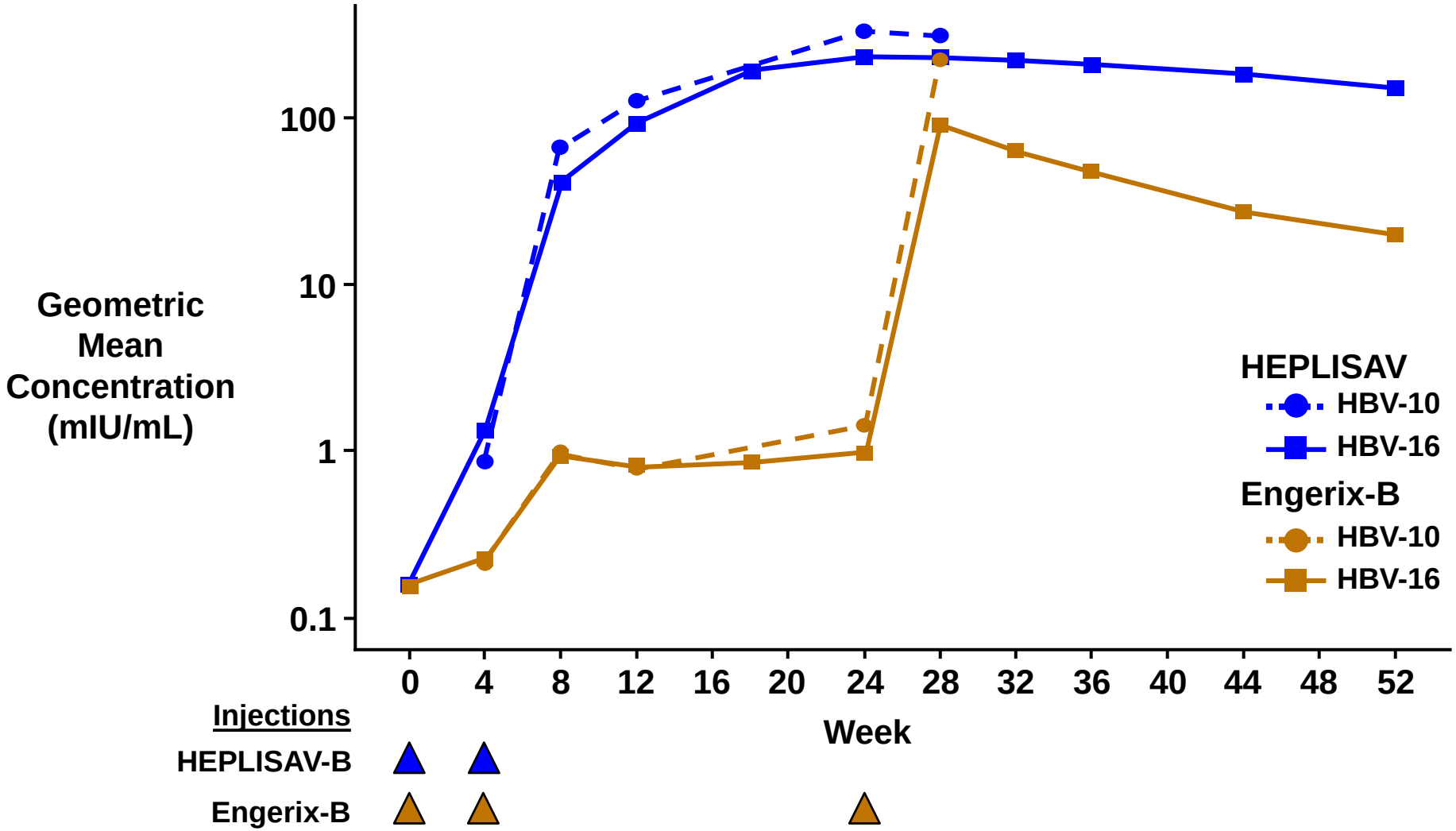
HEPLISAV-B SPRs Post-Single Dose

TRIAL	N	Mean Age (years)	Week 4 or 8 SPR (%)
HBV-03	47	23	78.9
HBV-08 (0/8 Group)	23	27	69.9
HBV-04	205	50	29.7
HBV-05	42	51	34.8

Reverse Cumulative Frequency Plot of Anti-HBs Concentration for HEPLISAV Week 24 and Engerix-B Week 28 in HBV-16 and HBV-10 (PP Population)



2 Pivotal Trials: GMCs Higher or Similar for HEPLISAV-B vs Engerix-B



New-Onset AESIs Excluding Bell's Palsy

PSP (HBV-10, HBV-16 and HBV-23)	Age/ Sex	Last Active Dose	Days Since Last Active Dose	Immune Classification[a]
HEPLISAV-B[b] (N=9,365)				
Grave's (Basedow's) disease	41/F	2	44	Classical autoimmune / T cell
Vitiligo	69/M	2	2	Classical autoimmune / T cell
Granulomatosis with polyangiitis	54/F	2	73	Classical autoimmune / Ab
Erythema nodosum	62/M	2	20	Innate immune-mediated
Lichen planus	48/F	2	26	Innate immune-mediated
Alopecia areata	52/F	2	229	Innate immune-mediated
Polymyalgia rheumatic	68/M	2	292	Innate immune-mediated
Guillain-Barré syndrome	35/F	2	111	Molecular mimicry / Ab
Ulcerative colitis	46/F	2	221	Intermediate MHC-class I
Cavernous sinus syndrome / THS	68/M	2	292	Unknown
Engerix-B (N=3,867)				
Grave's (Basedow's) disease	30/F	2	78	Classical autoimmune / T cell
ANCA+ vasculitis	44/F	2	127	Classical autoimmune / Ab
Scleroderma				Innate immune-mediated
Raynaud's phenomenon	46/M	3	33	Vasospasm

[a] Koenig 2011. [b] HEPLISAV-B 2.4:1 randomization; THS = Tolosa-Hunt Syndrome

HBV-23: MAE Imbalances with 95% CIs that Exclude 1

	HEPLISAV-B N=5,587		Engerix-B N=2,781			
	n	%	n	%	Relative Risk	95% CI
					HEP-B/Eng-B	
Herpes zoster	38	0.68	9	0.32	2.10	(1.02 - 4.34)
					Eng-B/HEP-B	
Thyroid neoplasm	0	0	5	0.18	22.1	(1.22 – 399)
Pleurisy	2	0.04	7	0.25	7.03	(1.46 – 33.8)
Hypomagnesemia	2	0.04	6	0.22	6.03	(1.22 – 29.8)
Arthropod sting	3	0.05	8	0.29	5.36	(1.42 - 20.2)
Exostosis	6	0.11	14	0.50	4.69	(1.80 – 12.2)
Positional vertigo	3	0.05	6	0.22	4.02	(1.01 – 16.1)
Impaired glucose tolerance	4	0.07	7	0.25	3.52	(1.03 – 12.0)
Inguinal hernia	5	0.09	8	0.29	3.21	(1.05 – 9.82)
Tooth infection	17	0.30	17	0.61	2.01	(1.03 – 3.93)

Wald modified method used to calculate continuity corrected RRs and asymptotic 95% CIs for MAE with 0 events

HBV-23: MAE Imbalances with Relative Risk >6.0 and Incidence ≥ 1/1000

	HEPLISAV-B N=5,587		Engerix-B N=2,781			
	n	%	n	%	Relative Risk	95% CI
					HEP-B/Eng-B	
Excoriation	10	0.18	0	0	10.45	(0.61 – 178)
Wound	9	0.16	0	0	9.46	(0.55 – 163)
Lipoma	8	0.14	0	0	8.46	(0.49 – 146)
Acute myocardial infarction	14	0.25	1	0.04	6.97	(0.92 – 53.0)
Bipolar I disorder	6	0.11	0	0	6.47	(0.36 – 115)
					Eng-B/HEP-B	
Adenomyosis	0	0	3	0.11	14.1	(0.73 – 272)
Acute cholecystitis	0	0	3	0.11	14.1	(0.73 – 272)
Muscle rupture	0	0	3	0.11	14.1	(0.73 – 272)
Oral herpes	0	0	3	0.11	14.1	(0.73 – 272)
Irritable bowel syndrome	1	0.02	4	0.14	8.04	(0.90 – 71.9)
Oral candidiasis	1	0.02	4	0.14	8.04	(0.90 – 71.9)

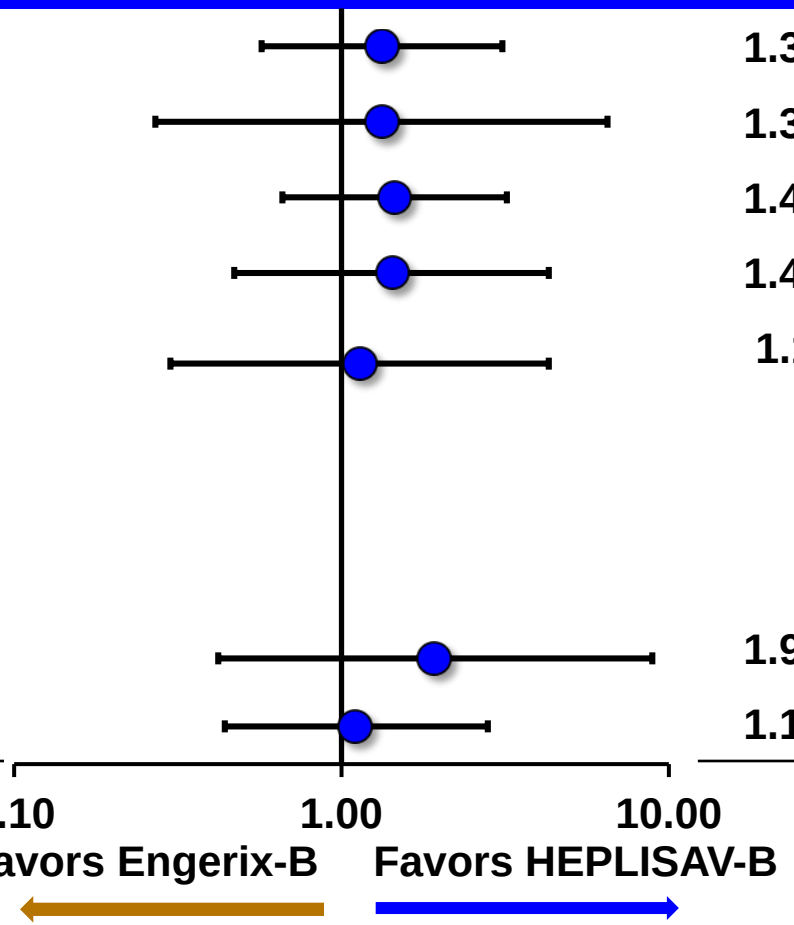
Wald modified method used to calculate continuity corrected RRs and asymptotic 95% CIs for MAE with 0 events

Potential Myocardial Infarctions from SMQ

PSP (HBV-10, HBV-16 and HBV-23) Preferred Term	HEPLISAV-B N=9,365		Engerix-B N=3,867	
	n	%	n	%
Subjects with ≥ 1 qualifying AE	21	0.22	4	0.10
Acute coronary syndrome	1	0.01	0	0
Acute myocardial infarction	16	0.17	2	0.05
Angina unstable	1	0.01	1	0.03
Coronary artery occlusion	1	0.01	1	0.03
Myocardial infarction	2	0.02	1	0.03

MACE by Cardiovascular Risk Factors

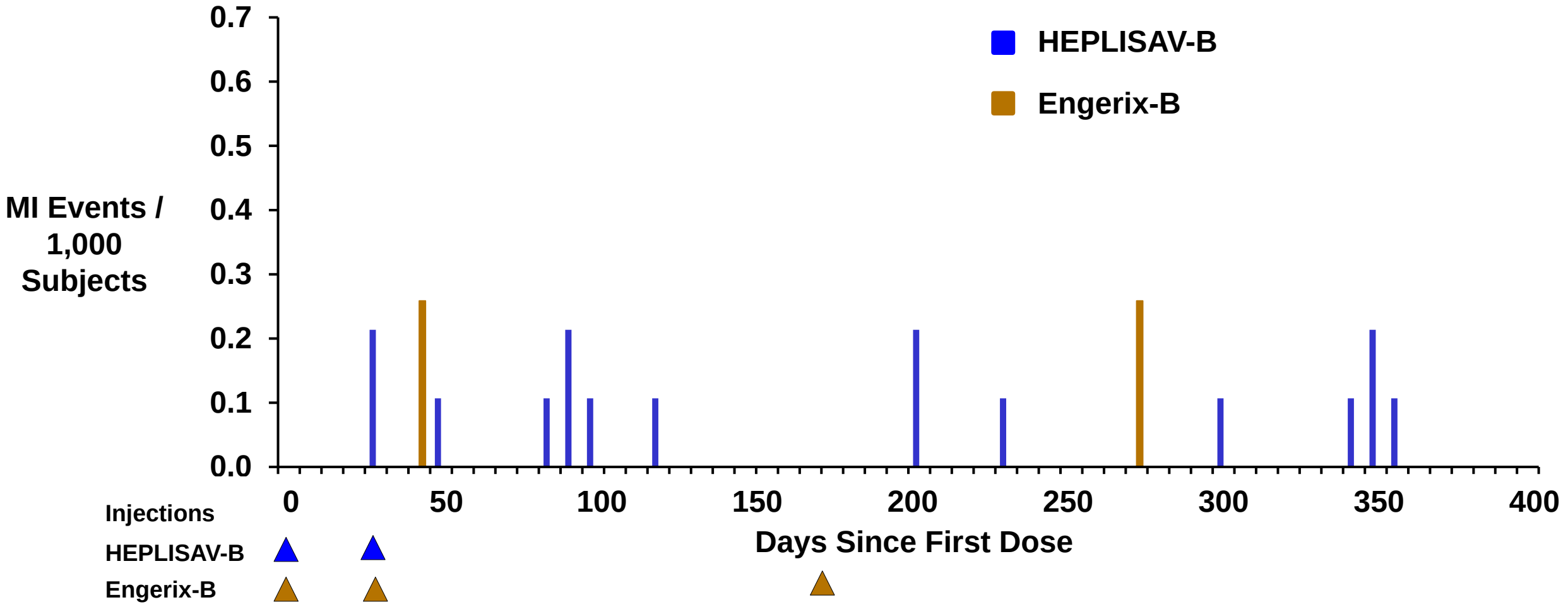
(PSP)	HEPLISAV-B N=9365 n/N (%)	Engerix-B N=3867 n/N (%)	Relative Risk (95% CI)
Hypertension	22/2792 (0.79)	7/1178 (0.59)	1.33 (0.57, 3.1)
Diabetes Mellitus	6/961 (0.62)	2/425 (0.47)	1.33 (0.27, 6.6)
Age	28/4692 (0.60)	8/1948 (0.41)	1.45 (0.66, 3.2)
Obesity	14/4050 (0.35)	4/1657 (0.24)	1.43 (0.47, 4.3)
Smoker	8/2928 (0.27)	3/1251 (0.24)	1.14 (0.3, 4.3)
Number of Risk Factors			
0	1/1531 (0.07)	0/590 (0)	NA
1	5/3160 (0.16)	0/1305 (0)	NA
2	9/2534 (0.36)	2/1081 (0.19)	1.92 (0.42, 8.9)
3+	16/2140 (0.75)	6/891 (0.67)	1.10 (0.44, 2.8)



Findings from Blinded Review of Clinical Summaries and Cardiac Catheterization Results

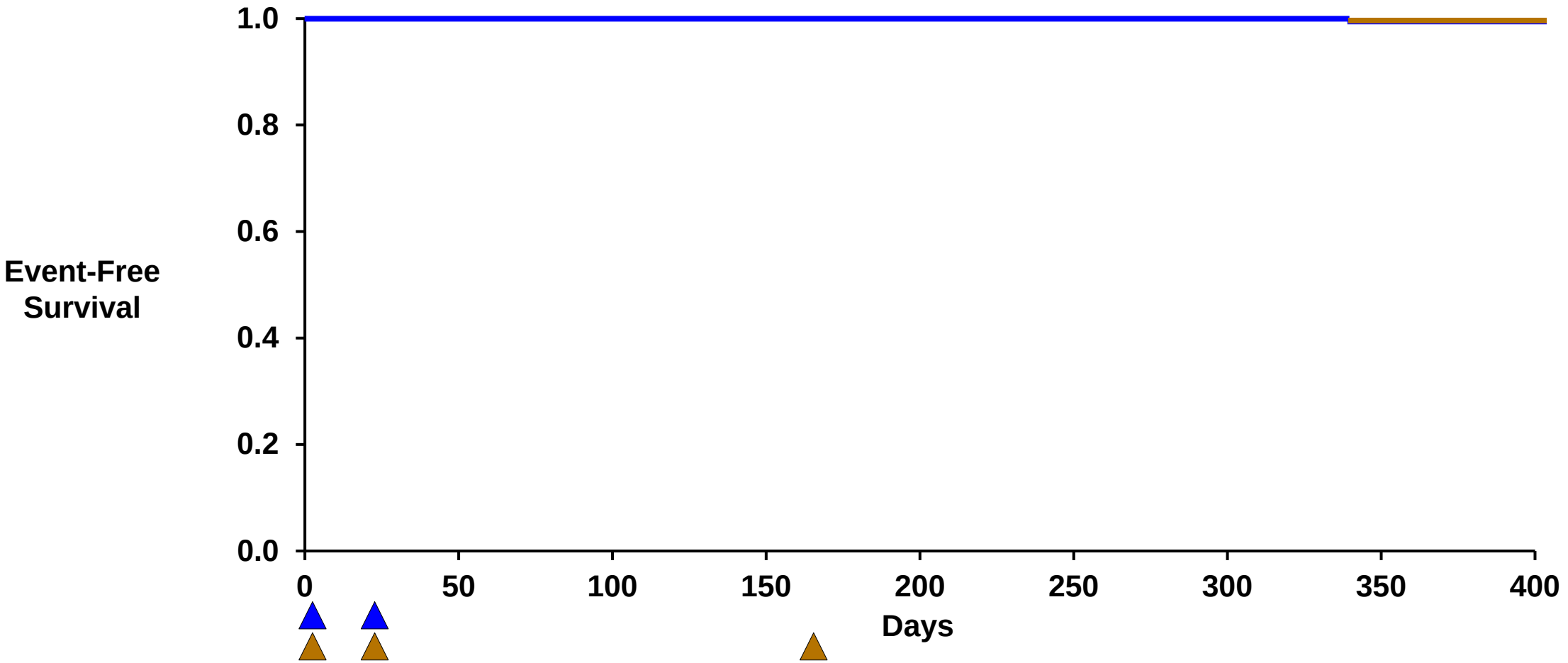
- Typical coronary event in nearly all cases
  - "Culprit" lesion
  - Advanced, multi-vessel obstructive disease
- No evidence of inflammation or immune cause
  - No vasculitis
  - No aneurysmal disease, dissection, vasospasm
  - No embolism / *in situ* thrombosis
  - No myocarditis
- No evidence of myocardial supply / demand mismatch

Confirmed MI Events Occurred Throughout Trials



Primary safety population

MACE Similar Between Groups Following Injections – Full Scale



Primary safety population